



NATURAL RESOURCES DEFENSE COUNCIL

Sept 12th, 2018

Thank you for the opportunity to provide comments to IARC staff and the IARC Advisory Group to Recommend an Update to the Preamble.

I am a senior scientist at the Natural Resources Defense Council (NRDC), a national, non-profit environmental organization of lawyers, scientists, and other professionals. I am also part-time faculty at George Washington University's department of environmental and occupational health. I have a master's degree and a PhD in anatomy and cell biology from the University of Saskatchewan and a postdoctoral certificate from the University of Maryland School of Medicine.

My work with NRDC requires a highly specialized expertise in U.S. chemicals policy. Much of my work is focused on understanding and explaining the science behind toxic chemical regulation and on advocating for regulations that are consistent with science, health policy, and environmental law. On occasion, I provide testimony and scientific briefings for members of Congress and US federal advisory committees. I also provide scientific support for NRDC litigation activities to enforce US environmental and right-to-know laws.

I have read and agree to the Code of Conduct for IARC/WHO experts. On behalf of NRDC I have expressed public positions on the scientific evidence of harm to human health and the environment from chemicals that are the subject of IARC research, review, and assessment. I have referenced IARC Monographs while providing scientific support for NRDC litigation to enforce environmental and right-to-know laws. On behalf of NRDC I have also advocated for IARC as an authoritative body to inform government activities. Neither NRDC nor I have any direct or indirect financial or fiduciary interest in the manufacture or sale of any chemical or agent that is the subject of the IARC monographs.

Thank you for the opportunity to provide comments on the IARC Monograph Preamble.

### **Current COI policy is appropriate**

In response to public concerns regarding financial conflicts among Working Group members, in 2006 IARC amended its preamble to implement an excellent public process to address conflicts of interest. Conflicts are to be disclosed and avoided but are not necessarily an eliminating factor for an expert. The reporting of conflicts in the final Monograph, accompanying each person's name and affiliation, is an important part of the Monograph conflict and disclosure policy. The existing policy is successful.

The IARC policies do not bar subject matter experts, even if they have direct or indirect financial conflicts. The main authors of studies sponsored by industry are sometimes included as specialty experts or Working Group members where their research is being considered by IARC. For example, in 2006 IARC reviewed formaldehyde (Volume 88), and invited specialists on the Working Group included: Rory Conolly of the Chemical Industry Institute of Toxicology (CIIT); David Eastmond who had funding from the chemical industry; and Steve Olin of the ILSI food and chemical industry trade association. The Final Monograph includes a footnote for each person identifying that they received funding from companies and trade associations with a direct interest in the subject matter of the meeting.

Industry representatives and others can also be invited to the Working Group meeting as non-voting observers, and can move freely among the subgroups, as well observe the plenary sessions. For example, at the 2015 IARC meeting to review some insecticides and herbicides (Vol 112), observers from Monsanto Company USA (Thomas Sorahan) and Cheminova were present throughout the week-long meeting. According to IARC Monograph rules, Observers cannot serve as Meeting Chair or Subgroup Chair, draft any part of a Monograph, or participate in the evaluations. They must also agree not to interfere or influence Working Group members either before or during the meeting; any Working Group member who is contacted inappropriately must report it.

There is no evidence that no-strings government funding, such as competitive research grants, constitute a conflict of interest since the funding is only awarded after a lengthy, rigorous, public, competitive process, and is given without any constraints on the results or outcome of the research. Importantly, the funder does not profit from the findings of the research.<sup>1</sup> Industry-sponsored research has none of those traits; it is more like a gift targeted to specific researchers for the purpose of obtaining pre-defined results. As Professor Dr. Lisa Bero writes: "Scientists cannot be separated from their interests or their social position in the world, but they can be free of financial conflicts of interest. Everyone has different individual interests, but industry sponsorship or investigator payments serve as a megaphone, amplifying and multiplying a set of interests, which align with the sponsor's, and thereby creating a widespread platform of influence from the sponsor".<sup>2</sup>

IARC should continue to apply its conflict and disclosure guidelines as it has been doing.

### **Current policy of treating draft and deliberative information as confidential is preferable**

Some members of the regulated community, and US Congressional Republicans, have suggested that the Monograph Programme make all its working group drafts and revisions available to the public. This

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<sup>1</sup> Bero L. Ten tips for spotting industry involvement in science policy. Tob Control. 2018 Jun 25.

<sup>2</sup> Bero L. Ten tips for spotting industry involvement in science policy. Tob Control. 2018 Jun 25.

would be inappropriate as IARC's format is a deliberative process where drafts evolve through discussion and peer review.<sup>3</sup> Such drafts are not representative of the full group or of the IARC. Publicly releasing incomplete draft portions of the assessment before they have undergone full vetting and quality assurance by the Working Group would simply allow critics to politicize the process by cherry-picking and elevating portions of an assessment that depict a misleading picture when presented out of context. It is for similar reasons that the US National Research Council committees do not share deliberative or draft work products, routinely noting that: "the review comments and draft manuscript remain confidential to protect the integrity of the deliberative process" ([NRC 2011 formaldehyde preamble](#)).<sup>4</sup>

Because interested stakeholders may attend the Working Group meeting, and there is a public summary within days, a more detailed report in a month, and the full book-sized report within a year, there can be no legitimate reasons for wanting access to deliberative and pre-publication documents.

**Preamble should evaluate studies according to its existing quality criteria. Monograph chemical evaluations should expand the risk of bias analysis to include studies sponsored by the regulated industries**

Professor D. Michaels, former Assistant Secretary of U.S. OSHA, writes that, "Defending hazardous chemicals has become lucrative business. It is increasingly common for scientific studies to be commissioned in order to be deployed in regulatory or legal proceedings." IARC and other regulatory and public health agencies must beware of these publications by sponsors with financial interests in the study outcome.

Industry-sponsored research is like a gift targeted to specific researchers for the purpose of obtaining pre-defined results. This can lead to biased study design, biased study conduct, and biased reporting of study results – all with a favorable outcome for the sponsor.<sup>5</sup> For example, a survey of the pharmaceutical company funding on clinical research concluded that, "Bias in favour of industry is apparent in every one of the themes examined with the result that research funded by industry undermines confidence in medical knowledge."<sup>6</sup> Medical journals are extremely concerned about industry-bias leading to poor quality or even inaccurate studies, and have worked hard to tighten up their disclosure requirements for authors, peer reviewers, and even editors of journals. The Institute of Medicine includes an extensive discussion of the problems of financial conflict in its report on systematic

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<sup>3</sup> The Monograph Programme asks its Working Group members to sign a confidentiality agreement, in which IARC emphasizes that information being shared for the purpose of conducting the cancer evaluations should be treated as confidential or proprietary.

<sup>4</sup> See IARC responses to the US Congress: [http://www.iarc.fr/en/media-centre/iarcnews/pdf/IARC\\_cResponse\\_Reuters\\_October2017.pdf](http://www.iarc.fr/en/media-centre/iarcnews/pdf/IARC_cResponse_Reuters_October2017.pdf); also, in [http://governance.iarc.fr/ENG/Docs/CPWild\\_Smith\\_Biggs\\_Lucas\\_20180111.pdf](http://governance.iarc.fr/ENG/Docs/CPWild_Smith_Biggs_Lucas_20180111.pdf): "With respect to the confidentiality of deliberative documents, we note that reports from the US National Research Council routinely indicate that, 'the review comments and draft manuscript remain confidential to protect the integrity of the deliberative process'."

<sup>5</sup> Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. *Cochrane Database Syst Rev.* 2017 Feb 16;2:MR000033.

<https://www.ncbi.nlm.nih.gov/pubmed/?term=10.1002%2F14651858.MR000033.pub3>

<sup>6</sup> Lexchin J. Sponsorship bias in clinical research. *Int J Risk Saf Med.* 2012;24(4):233-42. doi: 10.3233/JRS-2012-0574.

review, citing recommendations of the International Committee of Medical Journal Editors that highlight relationships with commercial entities as of concern.<sup>7 8</sup>

IARC should beware literature reviews or meta-analyses, that are really industry propaganda pieces for the regulated industry sponsors. These are described by Dr. Michaels as, “little more than advocacy briefs made to resemble objective scientific papers” funded by product defense firms and regulated industries that “aim to impede public health regulation by questioning studies that have identified hazardous properties of asbestos, beryllium, chromium, lead and a host of other toxic chemicals”.<sup>9</sup> Similarly, Professor D. Kriebel finds that, “Consistent findings can strengthen confidence in the conclusions, as in the Health Effects Institute’s reanalysis of the Harvard Six Cities and American Cancer Society air pollution studies. But reanalysis can also create confusion and impede scientific progress if it is not done in the service of impartial inquiry.”<sup>10</sup> Dr. Michaels warns that, “Editors should be hesitant to accept them for publication in the peer-reviewed scientific literature.”<sup>11</sup> IARC and other regulatory agencies must be similarly guarded.

IARC should beware of the term ‘best available science’, which is defined by the chemical industry trade group, American Chemistry Council, as follows: “In evaluating best available science ... consider the peer review of the science, whether the study was conducted in accordance with sound and objective practices, and if the data were collected by accepted methods or best available methods.” (Beck, 2017).<sup>12</sup> IARC should not interpret this definition to mean Guideline studies required for regulatory product approval, or data that is collected according to the so-called Good Laboratory Practices (GLP) requirements imposed on industry product testing. Doing either would inappropriately favor industry studies, without assessing study quality at all.

No effect findings in regulatory studies conducted by industry according to pre-set methods are often pitted against adverse outcomes reported in hypothesis-driven academic research, in what is often called a “weight of evidence” exercise. However, these studies should be evaluated against IARC systematic review criteria, and not simply weighed against each other. Retired NIEHS scientist Dr. Jerry Heindel provides an excellent description of the distinction between academic studies and the regulated industry submissions: “When regulatory agencies assess the data on a chemical as part of their risk assessment they focus on two main types of studies. First are the Good Laboratory Practice, or GLP, studies: Let’s call them apples. They are standardized studies that use large numbers of animals, usually

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<sup>7</sup> Eden J., Levit L., Berg A.O., Morton S., editors. Finding what works in health care: standards for systematic reviews. The National Academies Press; Washington, D.C: 2011. p. 52

<sup>8</sup> Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. ICMJE, 2010.

<sup>9</sup> Michaels D. Addressing conflict in strategic literature reviews: disclosure is not enough. J Epidemiol Community Health. 2009 Aug;63(8):599-600.

<sup>10</sup> Kriebel D. Reanalysis: lessons great and small. Occup Environ Med. 2008 Jun;65(6):368-70. doi: 10.1136/oem.2007.034884.

<sup>11</sup> Michaels D. Addressing conflict in strategic literature reviews: disclosure is not enough. J Epidemiol Community Health. 2009 Aug;63(8):599-600.

<sup>12</sup> Written Statement of Nancy B. Beck, Ph.D., DABT Senior Director of Regulatory & Technical Affairs American Chemistry Council Before the U.S. Senate Committee on Homeland Security and Governmental Affairs Subcommittee on Regulatory Affairs and Federal Management Regarding a Hearing on the Agency Use of Science in the Rulemaking Process: Proposals for Improving Transparency and Accountability March 9, 2017. <https://www.americanchemistry.com/ACC-Senate-Testimony-on-Agency-Use-of-Science-in-the-Rulemaking-Process.pdf>

three doses of [the test] chemical, a standardized animal and standardized validated endpoints that include body weight, organ weights, estrus cyclicity, some hormones and histopathology. The second group of studies are those published usually by academic scientists: Let's call them oranges. These oranges use smaller numbers of animals (determined by statistical analysis), an animal model chosen for the study, a variety of doses from one to five or more (usually significantly lower than those used in the guideline studies), and many endpoints usually focused on site and molecular mechanisms and disease-related outcomes. Regulatory agencies, when assessing the data, always keep apples separate from oranges. The apples are considered high priority studies because they are standardized GLP studies. The oranges are considered as lower priority since the endpoints in many cases are molecular changes, that may not be considered adverse, and include a wide variety of novel and "non-validated" disease-specific endpoints."<sup>13</sup> This disturbing approach by regulated agencies produce chemical assessments that over-rely on the industry sponsored studies.

Guideline studies are conducted to gain regulatory approval of chemicals; they are sponsored by the regulated industry with an obvious financial interest in commercializing its product and reducing or avoiding regulatory restrictions. The guideline studies are required to follow specific off-the-shelf methods to make it easy for governments to evaluate them and to compare across studies. And, they must be compliant with Good Laboratory Practices (GLP) which describes how the study information is collected, recorded and reported. GLP requirements were imposed on industry regulatory studies following evidence of widespread animal abuses, fraudulent practices, and false reporting among industry testing laboratories. In many cases GLP and Guideline studies are not published, not subjected to public scientific scrutiny, and not independently peer reviewed.

Guideline studies are most often designed to identify major toxic effects (apical effects) like cancer, major organ weight gain or loss, body weight gain or loss, skeletal malformations, loss of fur, tremors and convulsions, diarrhea, and obvious signs of lethargy. However, by the time these major (apical) endpoints are observed, significant toxicity has already occurred. This is because Guideline studies must follow methods that are established over years of negotiated process between regulatory agencies and the regulated community, and thus almost by definition simply cannot reflect modern methods for evaluating chemicals. Guideline studies aren't designed to grapple with the issues of low-dose exposures, formulations and chemical mixtures, endocrine or hormonal effects, and subtle but significant neurobehavioral impacts like what are now known to be caused by even very low doses of lead during critical windows of development. In summary, Guideline studies are designed to observe obvious and significant toxicity, not to identify early warnings (upstream indicators) of potential harm, such as reduced anogenital distance which is a predictor of later-life infertility.

Rather than being subject to GLP and Guidelines requirements, academic research studies must instead adhere to the established standards of Institutional Review Boards (IRB) for both ethical and scientific conduct. Like many aspects of GLP guidelines, IRB's ensure that the studies are conducted according to established and evolving best practices and legal requirements for animal care, human subject protections, and other ethical practices. However, unlike GLP, the IRB does not mandate specific data collection or reporting requirements. And, unlike Guideline studies which hamstring researchers into pre-set methods, IRB review will provide guidance to sound research design while also encouraging cutting edge and exploratory research using novel methods to advance scientific knowledge.

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<sup>13</sup> Heindel J. The CLARITY Study: Integration of Apples and Oranges. Environmental Health News, Sept 10, 2018. <https://www.ehn.org/the-clarity-study-integration-of-apples-and-oranges-2601960282.html>

The Monograph Programme should continue to evaluate all studies similarly – according to its systematic review procedures - without any special treatment for or favoring of GLP or Guideline studies. It should expand its risk of bias analysis to include consideration of study sponsorship by the regulated industry, given its obvious financial interest in the study outcome and in the outcome of the Monograph assessment.

### **Avoid scoring studies**

It has been documented that the use of scoring or ranking studies, particularly to develop a composite score or to eliminate studies, will inevitably lead to a bias in study evaluation. This is because the scoring is based on pre-determined weighting strategies that fail to account for the complexity of study design, study conduct, how the study is being used, and other features. For example, JAMA reported that, “the use of summary scores to identify [clinical] trials of high quality is problematic.”<sup>14</sup> A medical journal review article titled, “No role for quality scores in systematic reviews of diagnostic accuracy studies” concludes that scoring systems simply don’t work.<sup>15</sup> A recent publication of 29 collaborators on new tools to assess risk of bias in systematic review specifically emphasized that they, “should not be used to generate a summary ‘quality score’ because of the well-known problems associated with such scores”.<sup>16</sup>

For all these reasons, the US Institute of Medicine specifically warns against scoring systems, and particularly against ones relying on reporting: “Quality scoring systems have not been validated. Studies assessed as excellent quality using one scoring method may be subsequently assessed as lower quality using another scoring method.”<sup>17</sup> Instead, the Institute of Medicine recommends an emphasis on risk of bias, so that the, “Systematic Review more appropriately assesses the quality of study design and conduct rather than the quality of reporting.”<sup>18</sup>

The current state of the science for evaluating clinical and environmental health research is to describe or document each component of the assessment tool separately, without trying to calculate an overall numeric score. The Monograph Programme should continue to evaluate studies according to its systematic review procedures, without introducing flawed scoring systems.

### **Providing summaries of all studies**

Those that do not support IARC have suggested that the Monograph Programme should be required to provide summaries of all the studies that are relevant to an assessment, even those that do not support the conclusions. However, the Monographs already do this with comments in square brackets as it

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<sup>14</sup> Jüni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. JAMA. 1999 Sep 15;282(11):1054-60.

<sup>15</sup> Whiting P, Harbord R, Kleijnen J. No role for quality scores in systematic reviews of diagnostic accuracy studies. BMC Med Res Methodol. 2005 May 26;5:19. Review.

<sup>16</sup> Whiting P, Savović J, Higgins JP, Caldwell DM, Reeves BC, Shea B, Davies P, Kleijnen J, Churchill R; ROBIS group. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol. 2016 Jan;69:225-34. doi:10.1016/j.jclinepi.2015.06.005. Epub 2015 Jun 16.

<sup>17</sup> Moher D, Jadad AR, Tugwell P. Assessing the quality of randomized controlled trials. Current issues and future directions. Int J Technol Assess Health Care. 1996 Spring;12(2):195-208. Review.

<sup>18</sup> Eden J., Levit L., Berg A.O., Morton S., editors. Finding what works in health care: standards for systematic reviews. The National Academies Press; Washington, D.C: 2011.

reviews every informative study including epidemiology or animal bioassays. The Working Group members review all publicly available studies and the working group provides short summaries. IARC also provides a transparent detailing of its systematic review process for study selection and evaluation. It will not improve the quality or quantity of IARC assessments if it must spend resources evaluating and summarizing studies that do not meet the IARC's criteria of a study of sufficient quality to be included in its assessment.

**Use of mechanistic information or alternative testing should be to upgrade a chemical hazard, not to weaken the standard**

IARC may update the Preamble to address mechanistic or mode of action information. To assist in the organization and use of newly acquired mechanistically-based information, some members of the scientific community are promoting development of an adverse outcome pathway (AOP) approach to systematically unify and evaluate new data streams in a biologically-relevant fashion. However, we caution IARC that while these may be useful as organizing principles, AOPs and other pathway-based processes (e.g., modes of action, mechanisms of action) can lead to false negatives (fail to protect human health) when used to evaluate the toxicity of chemicals with unknown and/or multiple ways to disrupt a cellular process.<sup>19</sup> Chemicals can act via different pathways depending upon the organ or system exposed to the agent being tested (e.g., tamoxifen inhibits cell proliferation in breast cancer cells but can stimulate proliferation in the uterus). Pathway-based approaches can also lead to increased amounts of bias – i.e., by favoring one mechanism over another – which can result in the exclusion of data and alternative mechanisms by which a chemical can cause harm.<sup>20</sup> For these reasons, these approaches are not appropriate for downgrading or dismissing evidence of toxicity, exposure, or risk.

**Use of models must be critically evaluated**

Modelled outputs are in many important ways like a meta-analysis or review article in that they incorporate the results of many studies to generate an overall summary of the data. Dozens or even hundreds of different pieces of information are put together to build models; the bias or error in those pieces will lead to bias or error in the model output. As such, models can be highly subjective, depending on the bias of the sponsor and any financial interests they may have in the regulations that may result. It is therefore critical that these models be publicly available and able to be used and tested by the scientific community and the public.

IARC should fully assess any models it uses for its chemical hazard assessments. In general, the following criteria should be applied:

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<sup>19</sup> See Comments to US EPA from the Natural Resources Defense Council on the Strategic Plan to Promote the Development and Implementation of Alternative Test Methods (Draft). Comment submitted by Kristi Pullen Fedinick. Docket EPA-HQ-OPPT-2017-0559-0573. May 11, 2018. <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2017-0559-0573>

<sup>20</sup> See Comments to US EPA from the Natural Resources Defense Council on the Strategic Plan to Promote the Development and Implementation of Alternative Test Methods (Draft). Comment submitted by Kristi Pullen Fedinick. Docket EPA-HQ-OPPT-2017-0559-0573. May 11, 2018. <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2017-0559-0573>

- Use of models should be to fill in data gaps when trying to set protective regulations, but not to overturn observations from laboratory or epidemiological studies;
- Models can be highly subjective, depending on the bias of the sponsor, and therefore correspondence from models developed by different sectors should be considered;
- The underlying assumptions that are used to build the model framework and are used to define the parameters of the model should be stated and carefully evaluated in the review;
- Any known limitations in the model should be stated;
- Appropriate and inappropriate uses of the model should be stated;
- Results of uncertainty and sensitivity analysis and validation tests should be provided;
- Application niche of the model should be stated;
- Proprietary models must be extremely well documented, if used.

We suggest that thorough documentation be provided of the underlying assumptions that are used to build the model framework and are used to define the parameters of the model. Model parameters are terms in the model that are fixed during a model run or simulation but can be changed in different runs to conduct sensitivity analysis or calibrate the model. Parameters can be quantities estimated from sample data to characterize a statistical population or known mathematical constants. For example, a pharmacokinetic model will build in assumptions regarding different pharmacokinetic algorithms such as breathing rate, heart rate, body size, diet composition, etc. While mathematical values for physiologic parameters may be built into the model, in fact, they may differ widely among people of different ages, life stages, genetic backgrounds, health status, etc. Broad assumptions about genetic differences and variations in enzymatic activity may be reasonable but may not adequately reflect sensitive populations of interest. While a model may reflect an average person, of average age and average weight, it may fail to represent the most vulnerable members of the population. Only by explicit documentation of the assumptions built into the model framework, can quantitative estimates of how closely a model captures sensitive individuals be performed. This is but one example of why it is critical to document the assumptions built into the framework of any model used by IARC.

#### **Criticism of IARC follows Tobacco playbook – Preamble should disclose and consider funding bias**

In 2015 IARC drew tremendous unwarranted criticism from agrichemical corporate interests over its classification of the herbicide glyphosate into Group 2A. However, this is not the first chemical assessment to be unjustly attacked by regulated industries, and it surely won't be the last. As Professor Dr. Jonathan Samet (USC) wrote in an article titled, "The IARC monographs: critics and controversy," industry criticisms of IARC follow the playbook of the tobacco industry as it sought to discredit findings linking smoking to cancer.<sup>21</sup>

Unlike IARC, the US Environmental Protection Agency's pesticide office is following Monsanto's approach to cancer assessment, dismissing each study that reports treatment-related tumors, ultimately classifying glyphosate as 'not likely' to cause cancer (EPA 2017). Monsanto has been quick to try to cast IARC's assessment as an outlier, when in fact EPA's cancer assessment failed review by its Agency cancer

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<sup>21</sup> Samet JM. The IARC monographs: critics and controversy. Carcinogenesis. 2015 Jul;36(7):707-9.



experts ([see NYTimes on the Cogliano Memo](#)),<sup>22</sup> and its external scientific advisory panel ([SAP 2017, p. 48](#)).

Monsanto is also citing the reports of two European agencies that are involved in approving pesticides for use on food crops, the European Food Safety Authority (EFSA), and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR). Neither JMPR nor EFSA linked glyphosate in the diet to cancer risk. But, IARC didn't look at just diet exposure from food and drinking water. Instead, IARC looked at all the available data, from all sources of exposure, including from handling or spraying the pesticide. Additionally, IARC wouldn't include studies that were unpublished or unavailable to the public, whereas the European food agencies included unpublished Monsanto studies, which were never subject to peer review or public scrutiny. In summary, the European food assessments—based largely on unpublished Guideline and GLP Monsanto studies — lack public transparency and in any case are irrelevant to the occupational and other non-dietary exposures of farmworkers and chemical handlers. The over-reliance on unpublished Guideline and GLP Monsanto studies by the U.S. and E.U. regulatory agencies is alarming, given the evidence that sponsorship by the regulated industry is linked to study bias favoring the sponsors' interests (see discussions detailed above on the COI policy).

In summary, IARC's method for study evaluation and data integration is consistent with US EPA Cancer Guidelines, and with global best practices for systematic review and chemical assessment such as approaches advanced by the U.S. National Academy of Sciences (NRC 2018),<sup>23</sup> the U.S. National Toxicology Program,<sup>24</sup> the international scientific collaboration that developed a framework for the "systematic review and integrated assessment" (SYRINA) of endocrine disrupting chemicals,<sup>25</sup> and the Navigation Guide systematic review method (NavGuide) developed by a collaboration of scientists led by the University of California San Francisco.<sup>26</sup>

As it updates its Preamble, the Monograph Programme should continue to align with these systematic review frameworks.

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<sup>22</sup> USEPA. Internal email from Vincent Cogliano to Norman Birchfield, December 7, 2015. EPAHQ\_0000206.

<https://assets.documentcloud.org/documents/4641115/Cogliano-Memo.pdf>

NYTimes. Pesticide Studies Won E.P.A.'s Trust, Until Trump's Team Scorned 'Secret Science' Backed by agrochemical companies, the current administration and Congress are moving to curb the role of human health studies in regulation. Danny Hakim and Eric Lipton. August 24, 2018.

<sup>23</sup> National Academies of Sciences, Engineering, and Medicine. 2018. Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation. Washington, DC: The National Academies Press.

<https://doi.org/10.17226/25086>.

<sup>24</sup> National Toxicology Program. Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. In: U.S. Department of Health and Human Services, editor.: Office of Health Assessment and Translation, Division of National Toxicology Program, National Institute of Environmental Health Sciences; 2015

<sup>25</sup> Vandenberg LN, Ågerstrand M, Beronius A, Beausoleil C, Bergman Å, Bero LA, Bornehag CG, Boyer CS, Cooper GS, Cotgreave I, Gee D, Grandjean P, Guyton KZ, Hass U, Heindel JJ, Jobling S, Kidd KA, Kortenkamp A, Macleod MR, Martin OV, Norinder U, Scherlinger M, Thayer KA, Toppari J, Whaley P, Woodruff TJ, Rudén C. A proposed framework for the systematic review and integrated assessment (SYRINA) of endocrine disrupting chemicals. *Environ Health*. 2016 Jul 14;15(1):74. Review.

<sup>26</sup> Woodruff TJ, Sutton P. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. *Environ Health Perspect*. 2014 Oct;122(10):1007-14. doi:10.1289/ehp.1307175. Epub 2014 Jun 25. Review.

## Corporate product defense strategy conflicts with public health agency

IARC has long been the target of criticism from chemical manufacturers and the regulated industries whose products are the subject of Monograph evaluations. However, the expanded chemical product defense strategy now includes US Congressional Republicans, the White House, and federal agency political appointees. Pending voting by the US Congress, it includes:

- Attempts to discredit and defund chemical assessment programs like IARC;
- Re-classification of government-funded scientists as having financial conflicts, blocking them from service on federal advisory committees while permitting industry representatives;
- Excluding peer-reviewed studies from regulatory consideration because complete datasets are not made public or they fail to follow the chemical industry definition of 'best available science' while favoring industry-sponsored guideline studies that are often not published or otherwise publicly available, so cannot be independently reviewed.

The scientific community has voiced opposition to these regressive policies. A Joint Statement of scientific journal editors from Science, Nature, PLOS journals, PNAS, and Cell raised alarm that political or policy measures that restrict the use of science will compromise resulting scientific assessments: "It does not strengthen policies based on scientific evidence to limit the scientific evidence that can inform them... Excluding relevant studies simply because they do not meet rigid transparency standards will adversely affect decision-making processes."<sup>27</sup>

IARC – as a public health agency – must continue to conduct its chemical assessments using all available information, evaluated with its systematic review framework that meets globally established best practices.

## Conclusion

In 2006, only a year before he sadly passed away, Dr. Lorenzo Tomatis, former Director of IARC and Chief of the Monograph Programme, author of over 350 articles, ten books, and the orange colored Monographs, chose to use his speech as recipient of the prestigious Ramazzini Award to remind IARC of the importance of primary cancer prevention. Dr. Tomatis warned IARC that it has often taken much too long to upgrade a chemical from a Group 2 (2B possible or 2A probable human carcinogens), to a Group 1 (known) which almost always requires epidemiology evidence. He lamented the failures to prevent cancer deaths when IARC waits so long to upgrade a chemical. He noted that adverse effects from extremely low doses of endocrine disruptors like bisphenol A, phthalates, and atrazine deserve attention. He reminded us of the example of formaldehyde, that not only took many years to move from Group 2 into Group 1, but also that the classification is only for certain types of tumors but not others. Dr. Tomatis argued that, "If the validity of the precautionary principle is not accepted, type 2B situations will create an impasse of which the only outlet is the official perpetuation of risk conditions with

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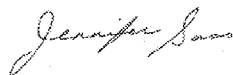
<sup>27</sup> Berg J, Campbell P, Kiermer V, Raikhel N, Sweet D. Joint statement on EPA proposed rule and public availability of data. Proc Natl Acad Sci U S A. 2018 Jun 12;115(24):6098.

Pentagon fires a warning shot against EPA's 'secret science' rule. Science magazine. By Sean Reilly, E&E News Aug. 28, 2018. <http://www.sciencemag.org/news/2018/08/pentagon-fires-warning-shot-against-epa-s-secret-science-rule>

possible ominous consequences on health.”<sup>28</sup> In other words, data gaps and uncertainties should be addressed so as to avoid false negative conclusions re the toxicity of chemicals, consistent with World Health Organization’s goal of preventing the global burden of cancer.<sup>29</sup>

In his closing remarks, Dr. Tomatis warned that, “a key role in the protection of public health will be played by an action aimed at banning or sharply decreasing the presence of noxious chemical in our environment. If we ... want to implement efficient primary prevention, conscious of the responsibility we have toward the present but also future generations, we should seriously consider all the various components of risk that have until now been unjustifiably underestimated or ignored.”<sup>30</sup> The IARC Monograph’s role providing authoritative assessments of carcinogenic agents is critically important for informing public health policies and practices around the world. IARC plays a critical role in providing the scientific information and evaluations to support evidence-based primary prevention policies. Where governments and industries take protective action based on IARC Monograph cancer assessments, much suffering may be avoided, and many lives saved.

Respectfully,



**Jennifer Sass, Ph.D.**

*Senior Scientist, Natural Resources Defense Council  
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